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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,432	07/20/2001	Jacob Waugh	13720-105065US1	2657

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

usptomailnyc@kslaw.com

Office Action Summary	Application No.	Applicant(s)	
	09/910,432	WAUGH ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *17 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-85,87-90 and 139* is/are pending in the application.

4a) Of the above claim(s) *42-85* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *40, 41, 87-90, 139, and 140* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received on 11/17/08.

Claims 40-85, 87-90, 139 and remain pending.

Claims 42-85 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Election was made without traverse in a telephone conversation on 5/8/2008, and confirmed in the response of 11/17/08.

Claims 40, 41, 87-90, 139, and 140 are under consideration.

This Action is NON-FINAL due to new grounds of rejection not necessitated by amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40, 41, 139, and 140 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kayyem et al (WO 96/11712) in view of Yan et al (US 7,008,924) Foster et al (US 5,989,545), and Kabanov et al (Adv. Drug Del. Rev 30: 49-610, 1998).

Kayyem taught cell-specific delivery vehicles comprising a oppositely charged polymers. In one embodiment of the invention, a delivery vehicle is provided comprising a) a first polymeric molecule having a net positive or negative charge, b) at least one

second polymeric molecule having a net charge opposite that of the first polymeric molecule and complexed with the first polymeric molecule, the second polymeric molecule having attached thereto at least one cell targeting moiety, and c) at least one physiological agent attached to the first or second polymeric molecule (see Figs. 1 A and 1 B) or to a third polymeric molecule (see Fig. 1 C), wherein the third polymeric molecule, if present, has a net charge opposite that of the first polymeric molecule and is complexed with the first polymeric molecule. See abstract; Fig. 1C; page 5, lines 3-11; and page 17, lines 5-17. The physiological agent could be a therapeutic agent that has a physiological effect on the cell to which it is delivered. See page 14, lines 20-22. Fusogenic peptides, and peptides that facilitate translocation between intracellular compartments may be attached to the polymers. See page 23, lines 15-27.

Thus Kayyem fairly taught a composition comprising a cationic polymer complexed to a plurality of anionic polymers wherein the anionic polymers comprised attached targeting agents and therapeutic agents. The compositions can also comprise a fusogenic peptides or nuclear localization peptides. Kayyem taught that the complexes should be “approximately electrically neutral, since electroneutrality is generally necessary to achieve high transfection efficiency” (page 10, lines 4-6, citing Wagner (1991)).

Kayyem did not teach composition wherein a cationic polymer covalently attached to a plurality of amino acid sequences of SEQ ID NO: 20, or the use of botulinum toxin as a therapeutic agent, and did not specify a net positive charge.

Yan taught conjugates comprising peptides of the sequence YGRKKRRQRRR or GGGGYGRKKRRQRRR. See; column 35, lines 22-33. Yan taught that such Tat peptides were peptide transduction domains that facilitated internalization of attached molecules into a cell. See column 35, lines 22-55.

Foster taught that botulinum toxin was useful as a therapeutic agent, and that it could be covalently linked to a targeting ligand. See abstract; and e.g. claims 1-11.

It would have been obvious to one of ordinary skill in the art at the time of the invention to attach a peptide of SEQ ID NO: 20 to the cationic polymer of Kayyem in order to facilitate cellular uptake of the complex. One would have been motivated to attach the peptide to the cationic polymer because the peptide is strongly cationic, and the invention of Kayyem depends on the interaction of oppositely charged polymers to form a complex. Accordingly, one of ordinary skill when deciding which polymer to attach the peptide to, would opt to place it on the like-charged cationic polymer in order to avoid interfering with the charge interaction between the cationic and anionic polymers.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use botulinum toxin as a therapeutic agent in the invention of Kayyem because it is readily apparent that the composition of Kayyem is useful for delivery of therapeutic agents generally to cells, because botulinum toxin was a well recognized therapeutic agent, as evidenced by Foster, and because Foster showed that botulinum toxin could be conjugated to targeting agents without loss of activity.

Regarding the charge of the complexes, Kayyem taught that they should be "approximately electrically neutral, since electroneutrality is generally necessary to achieve high transfection efficiency". So the teaching of Kayyem appears to allow for slightly negative, slightly positive, and neutral complexes. The prior art taught that the charge of interpolyelectrolyte complexes (ionic complexes between polycationic and polyanionic macromolecules) was a result-effective variable. Kabanov reviewed interpolyelectrolyte complexes for gene delivery, i.e. complexes between polycations and polyanionic nucleic acids. Regarding net charge, Kabanov indicated that polycation/DNA complexes are soluble only if there is an excess of either DNA or polycation, so that non-stoichiometric complexes are formed, which are either negatively charged (DNA excess) or positively charged (polycation excess). The negatively charged complexes, with an excess of plasmid DNA, are inactive in eukaryotic cells. The stoichiometric (neutral) complexes precipitate and cannot be used in pharmaceutical formulations. The cationic complexes having an excess of a polycation can be produced that are both stable in solution and transfect cells. See page 50, right column, second full paragraph.

In view of these teachings, one of ordinary skill at the time of the invention would, at a minimum, have been motivated to avoid precisely electroneutral complexes with the thermodynamically reasonable expectation that such complexes would be insoluble. It is not immediately clear that the inactivity of the negatively charged nucleic acid complexes of Kabanov would convey to negatively charged complexes of Kayyem in which the "active" ingredient is not a nucleic acid. Nonetheless, in view of teachings of

Kabanov, one of ordinary skill in the art at the time of the invention would have found motivation to assay complexes that retained enough of a charge, positive or negative, to remain soluble. Further, one would have considered using a ratio of polycation to polyanion that provided positively charged particles simply because Kabanov indicated that these were soluble stable and active. In view of the fact that the solution to the problem of maintaining complex solubility, and activity of the drug, lay in forming a complex with either a positive or negative net charge, it would have been obvious to try either negatively or positively charged complexes because these two possibilities represent a finite number of predictable potential solutions. Finally, because the prior art showed that particle charge was a result-effective variable, it would have been obvious to optimize the charge in order to maximize activity.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 11/17/08 have been fully considered but they are not persuasive.

At pages 13-14, Applicant argues that the cited references fail to teach a positively charged complex. This argument was persuasive as regards the rejection in the previous Action, but is addressed fully in the rejection set forth above.

At page 14, Applicant argues that Kayyem teaches away from the claimed invention by requiring significant electroneutrality. This is unpersuasive, the language of Kayyem requires only that the charge of the complexes be near neutral, not precisely

neutral. Kayyem therefor allows for somewhat positive and somewhat negative complexes that are near neutral. As discussed above, a precisely electroneutral complex would be expected to be insoluble based on the teachings of Kabanov.

Applicant argues at pages 15-18 that the proposed combination of references improperly changes the principle of operation of Yan. Applicant asserts that Yan reports the use of the HIV-TAT fragment YGKKRRQRRR only in the context of directly attaching to the fragment by covalent bond to the therapeutic or imaging agent to be delivered to the cell. This is unpersuasive. The basic principle of operation of the TAT peptide, as related by Yan, is that it is a protein transduction domain (PTD) that can be used to internalize proteins into a cell. Kayyem explicitly taught that the polycation of the invention could be a polypeptide (see page 10, lines 15-26. Therefore attachment of the protein transduction domain of the invention of Yan to any of the polypeptide polycations of Yan would not affect the principle of operation of the transduction domain. Further, Applicant has presented no evidence that the principle of operation of the PTD would be affected in any way by the formation of a complex between the polypeptide to which it is attached and one or more polyanions. On the other hand, Kayyem disclosed that delivery of nucleic acid/polylysine complexes was improved by conjugation of fusogenic peptides to polylysine (page 4, lines 2-6). Note that the TAT peptide YGKKRRQRRR was considered by those of skill in the art at the time of the invention to be a fusogenic peptide. See Boulikas, US 6,511,676, at column 13, lines 19-22. Accordingly the preponderance of evidence of record suggests that attachment of the TAT PTD to a polycationic polypeptide in the invention of Kayyem would not

constitute a change in the principle of operation of the PTD as disclosed by Yan. The PTD would still be expected to function to facilitate transduction of a protein across a membrane.

Applicant asserts at page 16 that a faithful reading of Yan would suggest directly attaching the TAT peptide to a targeting therapeutic or contrast agent of Kayyem. This is unpersuasive because Kayyem discloses that fusogenic peptides can be fused to polylysine in order to improve delivery of complexed nucleic acids. It is unclear, why6, in view of this disclosure, one of ordinary skill would limit their thinking in the way Applicant has suggested.

Applicant states at page 16 that, to their knowledge, there is no teaching in the prior art of the attachment of efficiency groups to a positively charged backbone to increase transport of a non-covalent complex comprising a positively charged backbone. However, Kayyem discloses this concept at 4, lines 2-6, which discusses the conjugation of fusogenic peptides to polylysine to improve transfection with DNA that is complexed to the polylysine. Accordingly Applicant's arguments are unpersuasive, and the rejection is held to be proper.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 40, 41, 87-90, 139, and 140 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 7-24, 30, 31, 33-50, 57, and 59-61 of copending Application No. 10/591,486. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The '486 application claims compositions comprising a biologically active protein and a carrier which comprises polymeric backbone having attached positively charged branching groups and which is present in an effective amount for transdermal delivery, wherein the association between the carrier and the biologically active protein is non-covalent. The polymeric backbone may comprise instant SEQ ID NO: 19 or 20 (see claim 31). It is clear from the supporting specification that these compositions may contain negatively charged polymers comprising botulinum toxin and targeting agents. Thus invention as a whole was prima facie obvious.

Claims 40, 41, 87-89, 139, and 140 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-3, 7-15, 29, 68-77, and

241-249 of copending Application number 10/793,138. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The '138 application claims:

A composition comprising a biologically active protein that is not insulin, and a carrier that is present in an effective amount for transdermal delivery of the biologically active protein, wherein association between the carrier and the biologically active protein is non-covalent, wherein the carrier comprises a positively charged backbone comprising a member selected from the group consisting of polyalkyleneimine, a positively charged polypeptide, a peptoid, an electronic mimic of a polypeptide and a steric mimic of a polypeptide; wherein the positively charged backbone comprises attached positively charged branching groups that are amino acid sequences selected from the group consisting of (gly)p-RGRDDRRQRRR-(gly)q (SEQ ID NO. 3), (gly)p-YGRKKRRQRRR-(gly)q (SEQ ID NO. 4), (gly)p-RKKRRQRRR-(gly)q (SEQ ID NO. 5), (gly)n1-(gly)n2 (SEQ ID NO. 2), gly3-arg7 (SEQ ID NO. 6), GGGRKKRRQRRR (SEQ ID NO. 7), and (gly)n3-(arg)n4 (SEQ ID NO. 1), wherein the subscripts p and q are independently an integer from 0 to 20, wherein n1 is an integer from 0 to 20 and n2 is an odd integer from about 5 to about 25, and wherein n3 is an integer from 3 to about 5 and n4 is an odd integer from about 7 to about 17.

The biologically active protein can be botulinum toxin. See claims 68-73 and 241-249. When read in view of the specification as filed, the claims embrace compositions comprising a cationic backbone and a biologically active protein that is

linked to a polyanion complexed to the polycation, as well as a second polyanion comprising a targeting agent. Thus invention as a whole was prima facie obvious.

Claims 40, 41, 87-90, 139, and 140 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 10-24, 30, 31, 33-50, 57, 59-61, and 63-66 of copending Application No. 11/073,307. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The '307 application claims compositions comprising a biologically active protein and a carrier which comprises polymeric backbone having attached positively charged branching groups and which is present in an effective amount for transdermal delivery, wherein the association between the carrier and the biologically active protein is non-covalent. The polymeric backbone may comprise instant SEQ ID NO: 19 or 20 (see claim 31). It is clear from the supporting specification that these compositions may contain negatively charged polymers comprising botulinum toxin and targeting agents. Thus invention as a whole was prima facie obvious.

Conclusion

No claim is allowed. Embodiments of the invention requiring SEQ ID NO: 19 are free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the

hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer, Ph. D./
Primary Examiner, Art Unit 1635